National Institute of Biomedical Imaging and Bioengineering

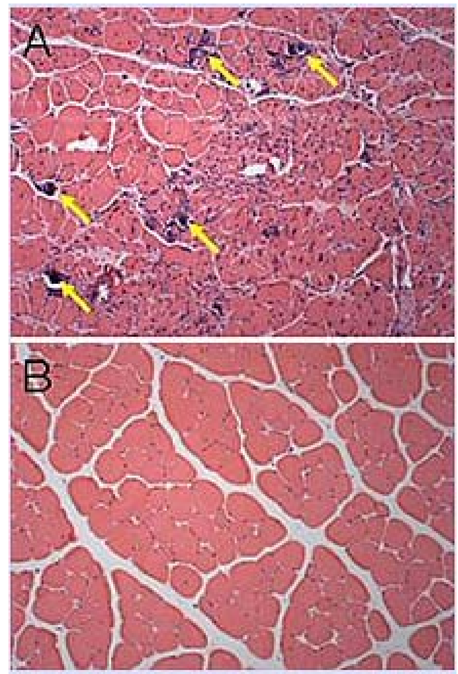
Polymer Library May Improve Gene Therapy for Cancer

A team of researchers combining expertise in materials science, chemistry, and cancer research has devised a new technique that caused 40 percent of prostate tumors in mice to shrink in initial experiments. The research marks a significant advance in a method known as suicide gene therapy, which delivers a deadly payload directly to tumor cells, causing them to self-destruct.

The team created a "library" of hundreds of polymers that might carry the genetic material to attack cancer cells, and then used automated screening techniques to zero in on the best candidates quickly.

More than half a million Americans die of cancer each year, despite advances in surgery, radiation therapy, and chemotherapy. Suicide gene therapy holds promise because it uses DNA to destroy specific cell types in the body.

But gene therapy for cancer is a tall order. It must deliver DNA treatments into cells and create a minimal amount of toxicity, while also not attacking healthy tissues. A roadblock to success is the lack of a safe and reliable technique for delivering DNA to specific cells. Viruses are often used as vectors to transport the DNA because they can infect cells effectively. Yet they also increase the likelihood of side effects such as potentially deadly allergic reactions. Recent research is focusing on nonviral carriers based on polymers, which may be safer but have been less reliable than a virus in carrying treatments to target cells.



New polymers like MIT's C32 may deliver drugs better than existing polymers used for gene therapy. In image A, a muscle injected with an older polymer and DNA shows calcification damage to cells (indicated by the arrows). In image B, a muscle injected with MIT's new C32 polymer and DNA does not show similar damage.
Photos courtesy of the National Academy of Sciences of the USA. Photos originally appeared in the Proceedings of the National Academy of Sciences. Copyright 2004.

Developing the Library

Much work remains to be done before the U.S. Food and Drug Administration approves a gene therapy for prostate cancer. However, researchers are making headway in identifying more potent toxins for specific cancers and creating better ways to get them inside cancer cells. For example, scientists funded by the National Institute of Biomedical Imaging and Bioengineering and the National Cancer Institute have collaborated on the development of a polymer called C32 that can carry the DNA of diphtheria toxin (DT) to prostate tumors and kill prostate cells in mice.

Their research represents several advances. A team led by Dr. Robert Langer at the Massachusetts Institute of Technology in Cambridge, Massachusetts, for the first time used high-throughput screening techniques to create a library of more than 500 polymers to be used as nonviral DNA vectors. The team collaborated with Dr. Janet Sawicki, a senior investigator at the Lankenau Institute for Medical Research in Wynnewood, Pennsylvania. Both teams found C32 to be the best-performing polymer to get DT to prostate cells. Sawicki identified DT as a promising therapy because it destroys both rapidly and slowly dividing tumor cells. In contrast, other suicide gene therapies go after only the fast-dividing cells, thus missing slower cancers like prostate tumors. Additionally, DT is one of the most potent toxins known.

"We've developed a novel approach to creating polymer gene therapy vectors, and we've applied it successfully in animal models to treating prostate cancer," says Langer, a professor of chemical and biomedical engineering at MIT. Dr. Daniel Anderson, a research associate on the MIT team, headed the effort to devise the unique method for creating the polymer library and a quick-screening technique to identify the most effective and least harmful polymers, both of which are key to the approach. Instead of spending a year or more developing one polymer, and then possibly finding it does not work, Langer's team can look at hundreds or even thousands of compounds and find the best polymer within days. "No one has ever done this for gene therapy," Langer says. "It's like having a library of books and being able to choose the best one."

Creating a Therapy

To make the treatment, researchers put C32 liquid polymer into a tube and add purified DNA, explains Sawicki, the Lankenau investigator and main collaborator with MIT. The DNA encodes part of the DT protein, so the toxin itself is not being used. The DNA has a regulatory region, or promoter, that tells the DT gene when to turn on, in this case only in prostate cells and not in liver or other cells. Interactions between C32 and DNA cause the DNA to condense and form nanoparticles. The result is a milky solution in the tube, which can be injected into a tumor grown from human prostate cancer cells directly below the mouse's skin or directly into the mouse's prostate during surgery. Tests of C32/DT therapy, both in the laboratory and in mice, show it kills prostate tumors at high levels while having no toxic side effects, the researchers say.

Sawicki initially used viruses as drug-delivery vectors, but she says that the DNA needed to be effective was so long it barely fit into the virus, and the promoters lost their specificity for the cells they were targeted to destroy. MIT's polymers looked like a promising alternative. "These are really unique polymers. They're biodegradable, nontoxic, and they transfect these prostate cells with a very high efficiency, just like a viral vector would," she says.

The researchers still have a lot of work ahead of them. So far, the C32/DT therapy destroys all prostate cells, not just prostate-cancer cells. The researchers would like to make the therapy more specific to cancer cells, which could take years. They also hope to use the polymers for treating other conditions, such as ovarian cancer or even influenza. One near-term application by Sawicki uses the same treatment for enlarged prostate, which affects most men age 60 or older and causes problems such as frequent urination. Experiments in mice have been promising, with mouse prostate cells dying only three days after treatment. "The beauty is that now that we have established this kind of scientific foundation, we can start applying it to different problems," Langer says.

Reference

Anderson DG, Peng W, Akinc A, Hossain N, Kohn A, Padera R, Langer R, Sawicki J. A polymer library approach to suicide gene therapy for cancer. Proc Natl Acad Sci USA 101: 16028-16033, 2004.